REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Claim 1 has been amended.

I. Rejection of Claim 1 Under 35 U.S.C. 112, First Paragraph

Claim 1 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner suggests that the claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that the phrase "not to exceed a total dose of 2 mg/kg each day" is not taught in the specification as filed. Although Applicants disagree with the Examiner's suggestion regarding the teaching of the specification as filed, in an earnest effort to advance the prosecution and facilitate allowance of the claim, Applicants have amended claim 1 to recite that the dose administered is 1 mg/kg. Support for the amendment to claim 1 can be found explicitly at page 8, lines 14-15 where it is stated "The dosage of methotrexate shown to be effective in these studies was low, 1 mg/kg." Accordingly, the claim as amended meets the requirements

of 35 U.S.C. 112, first paragraph. Withdrawal of this rejection is respectfully requested.

Claim 1 has been rejected under 35 U.S.C. 112, first paragraph, also as failing to comply with the written description requirement. The Examiner suggests that the claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that the phrase "into the spinal cord but not the brain" is a concept that was not present in the specification as originally filed. Applicants respectfully disagree.

As discussed in the previous response filed January 24, 2007, the basis for the amended claim 1 language "intrathecally into the spinal cord but not into the brain" is the knowledge of one of skill at the time the application was filed and as such is not required to be explicitly taught in the specification as filed. MPEP 2163 states "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." (Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94). Further MPEP 2163 states that "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even

if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." (Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972)). Therefore, contrary to the Examiner's assertion in the Office Action at page 6, there is no need to incorporate by reference the text of a human anatomy and physiology text book because it would have been well known to one of skill in the art.

As a result, again as discussed in the previous responses, support for the amendment to claim 1 can be found in the teachings of the general principles of human physiology and pharmacokinetics that intraventricular administration will not produce a local concentration of active drug in the spinal cord area that is anywhere near the same concentration as would be achieved with intrathecal administration. As discussed in the previous responses to Office Actions in this case, this is because, as taught in basic human anatomy and physiology texts (e.g., *Human Anatomy and Physiology*, Second Edition, Elaine N. Marieb (editor), Benjamin Cummings Publishing: Redwood City, CA, pages 404-405, starting at the second column on page 404) the circulation of cerebrospinal fluid through the brain ventricles is designed such that only a very small amount of the cerebrospinal fluid from the ventricles circulates into the

central canal of the spinal cord. As is taught in this text, "most enters the subarachnoid space" (see page 404, second column, line 3-4 of second paragraph). Therefore, intraventricular injection of methotrexate would result in only a small amount of circulation of the injected drug, via the cerebrospinal fluid, into the spinal cord. The drug instead would be considered as being injected into the brain when it is given intraventricularly. Further, following intraventricular injection, the concentration of methotrexate achieved would not be expected by one of skill in the art to be as high as could be achieved through direct administration into the spinal cord area via intrathecal administration. The subarachnoid space, as shown in Figure 12.20 on page 404 of the text cited above, is not the area touched through intrathecal administration. Most importantly, one of skill would understand that intraventricular administration leading to subdural circulation is referring to the subdural area of the brain NOT the spinal cord. This is again a basic anatomical feature that allows for separation of the brain and spinal cord areas in the body. Therefore, in amending the language of claim 1, Applicants have relied on support found in the general principles of physiology and anatomy that were well known andaccepted at the time the application was filed. Applicants further point out that contrary to the

Examiner's suggestion, Applicants are not relying on the concentration of methotrexate in CSF specifically but on the generally known fact that intrathecal administration leads to a higher dose in the spinal column than would intraventricular administration.

Clearly, claim 1 as amended meets the requirements of 35 U.S.C. 112, first paragraph. The Examiner has failed to consider that one of ordinary skill in the art would have the understanding of the difference of intrathecal versus intraventricular administration wherein intrathecal administration would be definition result in injection of drug "into the spinal cord but not into brain". Accordingly, withdrawal of this rejection is respectfully requested.

II. Rejection of Claim 1 Under 35 U.S.C. 103(a)

Claim 1 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberlain et al. (1998) and Biomethodology of the Rat (http://research.uiowa.edu/animal/print.php?get+rat). The Examiner suggests that Chamberlain et al. teach intraventricular administration of methotrexate at a dose of 2 mg daily (40 mg total dose) to patients with leptomenigeal metastases presenting with radiculopathy, and that the method of administering intrathecally would overlap with this method.

Further, the Examiner suggests that the reference on Biomethodology of the Rat teaches that a rat weighs about 250 g and thus the 1 mg/kg dose of the present invention would equate to about 0.8 mg given to a rat, while a 2 mg/kg dose would equate to about 1.6 mg given to the rat. Therefore, the Examiner suggests these references teach the limitations of claim 1. Applicant respectfully disagrees with the Examiner's conclusions regarding the cited references.

First, with regard to the teachings of dose and the extrapolation of dose from the teachings of the specification as filed to compare that dose to the teachings of Chamberlain et al., Applicants respectfully disagree with the Examiner's arguments regarding dose extrapolation from mg/kg body weight doses to mg doses, regardless of body weight. It is a general principle of pharmacology that if an effective dose is taught to be a dose in mg/kg body weight, then in order to extrapolate the dosing from a rat, the species taught in the specification as filed, to a dose that might be used in humans, the species of the Chamberlain et al. reference, the dose extrapolation would be done based on consideration of the difference in body weights, not by ignoring the body weight differences as has been suggested by the Examiner. In the Examiner's arguments, it is suggested that one of skill would simply take a 2 mg dose as given to a

human and then give it to a rat. However, this is NOT what one of skill in the art would do. This would not be done because one of skill would assume that that dose in a much smaller animal would produce toxicity that could be dangerous. The reverse is also true. One of skill would never take a 1 mg/kg dose in a rat and assume that that dose in mg, about 0.8 mg to the rat, would have efficacy in a human based on the large difference in body size of the human as compared to the rat. The Examiner is totally mistaken in suggesting that one of skill in the art would ignore well-established principles of dose extrapolation and ignore the differences in body size when extrapolating from a rat to humans or even the reverse extrapolating from humans down to rats (as the Examiner is doing in the instant case).

As discussed in the previous response dated January 24, 2007, Chamberlain et al. disclose only use of a 2 mg dose of methotrexate, intraventricularly, in humans to treat a form of metastatic cancer. Nowhere in this reference is it suggested or taught that the 2 mg dose could be modified and given to any other species on the basis of mg drug per kg body weight. Although it is true that methotrexate is often dosed on a mg/m2 basis in cancer therapy, this is NOT the case for drugs used to treat pain. This is because, as taught only in the specification as filed, one of skill would need to understand how efficacy

related to safety in any particular species. That is why the teaching of the specification as filed is clear in defining dose on a mg/kg basis, to allow one of skill to understand how to extrapolate doses across different species. Chamberlain et al., however, is silent on this issue and thus would not be used by one of skill to extrapolate from a 2 mg dose in humans, which they would understand to be a dose of approximately 0.029 mg/kg/day based on a 70 kg individual or 0.033 mg/kg/day based on a 60 kg individual, to a dose in a smaller animal such as a rat. The 2 mg dose of Chamberlain et al. is much lower than the dose range claimed in the instant invention and as such would not be obvious to one of skill in the art. Again as well, it must be remembered that it is a general principle of pharmacology that you extrapolate doses across species based on mg/kg not mg alone and not on mg/m2 for pain treatment. Therefore, one of skill would automatically convert the 2 mg dose of Chamberlain to its mg/kg dose and then dose another species based on that dose. Using this procedure, one of skill would administer a 2 kg animal a dose of 2 x 0.033 or 2 x 0.029 mg/kg which would be a dose of from 0.058 to 0.066 mg NOT 2 mg as suggested by the Examiner in the Office Action. Based on use of standard practice in the art of pharmacology, there is no overlap between any of the teaching

of Chamberlain et al. and any dose range claimed in the instant invention.

Second, with regard to the dose route differences, intrventricular versus intrathecal dosing, Applicants disagree with the Examiner's suggestion that Chamberlain et al. teach a route that makes the claimed invention obvious. As discussed *supra*, one of skill in the art would understand that intraventricular administration of a drug is a very different route of administration than intrathecal drug administration and, as such, that a drug administered by these two routes could be expected to have different dose-response curves for pharmacological activity solely related to the different areas of the body being reached by these two routes. Chamberlain et al., in teaching intraventricular administration, are targeting the brain with their drug, NOT the spinal cord. Again, this is all general knowledge of one of skill in the art and as such is not needed to be explicitly taught in the specification as filed. Moreover, it is general knowledge that would lead one of skill in the art to understand that Chamberlain et al. are not sufficient teaching for one of skill to expect success in the method of the instant invention as claimed.

In order to establish a *prima facie* case of case of obviousness, three basic criteria must be met. MPEP 2143.

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly the reference cited fails to teach or suggest the invention as claimed. The reference cited, in fact, teaches use of methotrexate to treat cancer NOT lower back pain with radiculopathy. Second, the paper teaches use of a much lower dose range and a different route of administration. Therefore, this reference fails to teach the limitations of the claim as amended and also fails to provide one of skill with an expectation of success. It is only with the specification in hand that one of skill would understand that intrathecal administration at a dose level of 1 mg/kg body weight would be effective for treating lower back pain with radiculopathy. Accordingly, this reference cannot make obvious the invention of the amended claim.

However, in an earnest effort to advance the prosecution of this case, Applicants have amended the language of claim 1 to recite that the method of the instant invention involves administration of a dose level of 1 mg/kg of methotrexate intrathecally. Support for these amendments to the claims is

found at pages 8 and 9 of the specification as filed. In that section it is stated that the dosage "shown to be effective in these studies was low, 1 mg/kg." (see lines 14-15). Therefore, even using the Examiner's faulty logic regarding dose extrapolation, this dose, 1 mg/kg, in a rat is only 0.8 mg and is not equivalent to the 2 mg dose administered by Chamberlain et al. Withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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